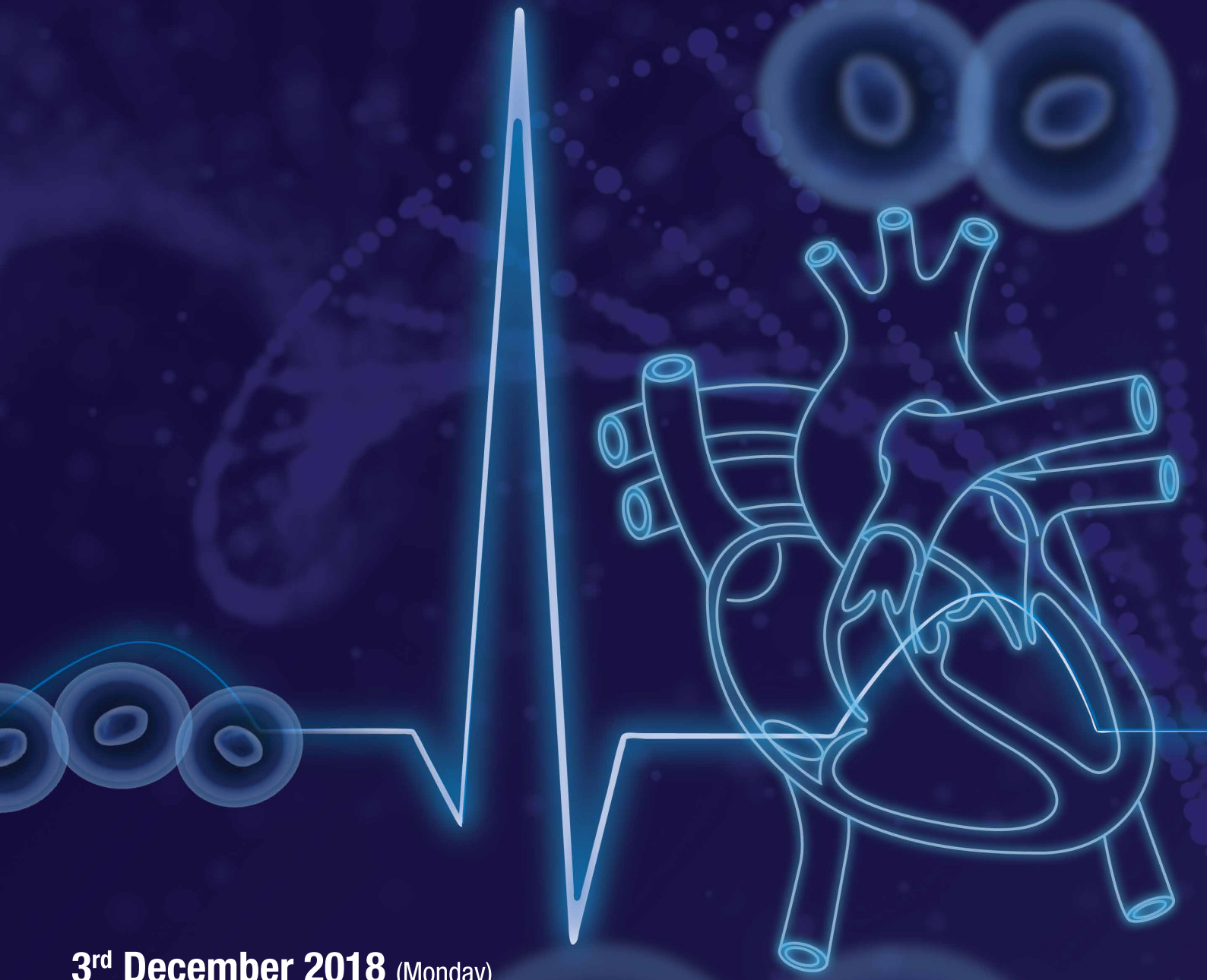
Human Pluripotent Stem Cell-based Precision Medicine and Therapies for Heart Diseases: **From Concepts to Realities**



3rd December 2018 (Monday)

Rayson Huang Theatre, The University of Hong Kong, Pokfulam Road, Hong Kong

Dr Li Dak-Sum Research Centre
李達三博士研究中心

Ming Wai Lau Centre
for Reparative Medicine
劉鳴煒復修醫學中心

Karolinska Institutet

Welcome Message

Dr. Li Dak-Sum Research Centre, The University of Hong Kong and Ming Wai Lau Centre for Reparative Medicine, Karolinska Institutet are pleased to welcome our friends and colleagues to the symposium entitled ‘Human Pluripotent Stem Cell-based Precision Medicine and Therapies for Heart Diseases: From Concepts to Realities’.

Following the success of the ‘Symposium on Regenerative Medicine for Heart Disease’ held in conjunction with the HKU-KI Course ‘Cell-based Heart Regeneration’ in Stockholm in 2015, this year’s symposium features a full day programme where leading scientists from the academia and industry around the world will meet and discuss a broad range of topics including cardiac regenerative medicine, novel bioengineering technologies, and translational bench to bedside regenerative medicine. We hope that this event will help foster tighter and broader collaborations on the development of stem cell technologies for tangible applications in drug development and regenerative therapies for heart diseases.

We thank you for your participation and hope you will enjoy productive interactions during the event.

Organisers

Yiu-fai Cheung
Bryan Lin Professor in Paediatric Cardiology
Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine
The University of Hong Kong

Ronald Li
Director
Ming Wai Lau Centre for Reparative Medicine, Hong Kong
Karolinska Institutet

Organising Committee

Yiu-fai Cheung
The University of Hong Kong

Wendy Keung
The University of Hong Kong

Ronald Li
Karolinska Institutet

Emily Ip
Karolinska Institutet

Thomas Leon
The University of Hong Kong

Gary Tse
The Chinese University of Hong Kong

Sponsors

Dr. Li Dak-Sum Research Centre, The University of Hong Kong

Ming Wai Lau Centre for Reparative Medicine, Karolinska Institutet

Programme Rundown

3rd December 2018 (Monday)

Time	Topic	Speaker
08:30	**REGISTRATION**	
09:00	**WELCOME AND OPENING REMARKS**	

Session I: Cell-Based Cardiac Therapies

09:15-09:45	**Gene therapy & genome editing for acquired and experimental heart failure**	**Roger Hajjar** Director, Cardiovascular Research Center Arthur & Janet C. Ross Professor of Medicine, Icahn School of Medicine at Mount Sinai
09:45-10:15	**The potential of human induced pluripotent stem cells to model and to treat congenital heart disease**	**Yiu-fai Cheung** Bryan Lin Professor in Paediatric Cardiology Clinical Professor, Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong
10:15-10:45	**Development of banking and testing protocols for GMP hiPSC**	**Jo Mountford** Head of Cellular Therapeutics, Tissues Cells and Advanced Therapies, Scottish National Blood Transfusion Service Hon. Associate Professor, Institute of Cardiovascular and Medical Sciences, University of Glasgow
10:45-11:15	**Predicting individual arrhythmogenic risk at the individual level using hiPSC**	**Jean-Sébastien Hulot** Team Leader, Clinical & Translational Investigation Center, Hôpital Européen Georges-Pompidou (Hôpitaux Universitaires Paris-Ouest) Paris Cardiovascular Research Center PARCC / INSERM
11:15-11:30	**COFFEE BREAK**	

Session II: Tissue Engineering and Drug Discovery

11:30-12:00	**Engineering cardiac tissue and development**	**Peter Zandstra** Director, School of Biomedical Engineering, The University of British Columbia
12:00-12:30	**A tissue-engineered scale model of the heart ventricle**	**Luke MacQueen / Kit Parker** Postdoctoral Fellow/Professor, Bioengineering in the Wyss Institute, Harvard University
12:30-13:00	**Small molecule drug discovery, transitioning from industry to academia: SERCA2a SUMO activators for heart failure**	**Robert DeVita** Director of Medicinal Chemistry, Drug Discovery Institute Professor, Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai

Time	Topic	Speaker
13:00-14:30	**LUNCH**	

Session III: Drug and Therapeutics Safety and Discovery in Industry

14:30-15:00	**Stem cell cardiomyocytes in drug discovery and development – are we there yet?**	**Bernard Fermini** Co-chair, CiPA Ion Channel Working Group of the U.S. Food and Drug Administration
15:00-15:30	**New challenges in safety pharmacology**	**Sonja Stoelzle-Feix** Director Scientific Affairs at Nanion Technologies Co-chair, CiPA Ion Channel Working Group of the U.S. Food and Drug Administration
15:30-16:00	**Toward a precision medicine approach to drug screening using Novoheart's hPSC-based MyHeart™ Platform**	**Kevin Costa** Co-founder and Chief Scientific Officer, Novoheart
16:00-16:30	**Collaborating to create engineered human tissues using 3D bioprinting technology**	**Tamer Mohamed** President and Chief Executive Officer, Aspect Biosystems
16:30-16:45	**COFFEE BREAK**	

Session IV: Commercializing Regenerative Medicine and Therapeutics

16:45-17:15	**Scale-up of pluripotent stem cell production to enable translation and commercialization**	**Emily Titus** Vice President, Technology Advancement, Centre for Commercialization of Regenerative Medicine (CCRM)
17:15-17:45	**Where is Hong Kong in developing precision medicine?**	**Sabrina Chan** Senior Executive Director, The Hong Kong Association of the Pharmaceutical Industry
17:45-18:00	**CLOSING REMARKS**	
19:00	**WELCOME DINNER FOR SPEAKERS**	

Roger Hajjar

Director, Cardiovascular Research Center

Arthur & Janet C. Ross Professor of Medicine, Icahn School of Medicine at Mount Sinai

Dr Hajjar is the Director of the Cardiovascular Research Center, and the Arthur & Janet C. Ross Professor of Medicine at the Icahn School of Medicine in New York, NY. He received his BS in Biomedical Engineering from Johns Hopkins University and his MD from Harvard Medical School and the Harvard-MIT Division of Health Sciences & Technology. He completed his training in internal medicine, cardiology and research fellowships at Massachusetts General Hospital in Boston.

Dr Hajjar is an internationally renowned scientific leader in the field of cardiac gene therapy for heart failure. His laboratory focuses on molecular mechanisms of heart failure and has validated the cardiac sarcoplasmic reticulum calcium ATPase pump, SERCA2a, as a target in heart failure, developed methodologies for cardiac directed gene transfer that are currently used by investigators throughout the world, and examined the functional consequences of SERCA2a gene transfer in failing hearts. His basic science laboratory remains one of the preeminent laboratories for the investigation of calcium cycling in failing hearts and targeted gene transfer in various animal models. The significance of Dr Hajjar's research has been recognized with the initiation and completion First-in-Man clinical trials in gene therapy for heart failure.

Dr Hajjar served as Director of the Cardiovascular Laboratory of Integrative Physiology and Imaging at Massachusetts General Hospital and Associate Professor of Medicine at Harvard Medical School. Dr Hajjar has also been a staff cardiologist in the Heart Failure & Cardiac Transplantation Center at Massachusetts General Hospital.

Dr Hajjar has won numerous awards and distinctions, including the Young Investigator Award of the American Heart Association. He was awarded a Doris Duke Clinical Scientist award and has won first prize at the Astra Zeneca Young Investigator Forum. He is a member of the American Society for Clinical Investigation. In 2012, he was awarded the Distinguished Alumnus Award from Johns Hopkins University, the Mount Sinai Dean's award for Excellence in Translational Science. He was awarded the 2013 BCVS Distinguished Achievement Award from the American Heart Association, the American College of Cardiology Paul Dudley lecture at the 2013 NY Symposium, and the Thomas W. Smith Lecture at the 2017 AHA.

He has authored over 450 peer-reviewed publications.

Dr Hajjar is the scientific co-founder of multiple biotechnology companies: Nanocor, Sumocor, and Cleavagen.

Gene therapy & genome editing for acquired and experimental heart failure

Our laboratory has developed a program of targeting important calcium cycling proteins in experimental models of heart failure (HF) by somatic gene transfer. This has led to a first-in-man phase 1 clinical trial of gene therapy for heart failure using adeno-associated vectors (AAV). Pulmonary hypertension (PH) is characterized by pulmonary arterial remodeling that results in increased pulmonary vascular resistance, right ventricular failure, and premature death. A clinical trial of inhaled AAV vectors carrying the cardiac isoform of the sarcoplasmic reticulum calcium ATPase is being planned the biological effects of such a strategy in patients with Pulmonary Hypertension.

Our group has been actively working on delivering CRISPR/Cas9 to correct a number of mutations in familial cardiomyopathies.

Funding: NIH R01 HL117505, HL119046, HL129814, 128072, a P50 HL112324, Transatlantic Fondation Leducq grant, and the Gene Therapy Resource Program of the NHLBI.

Speaker Bios & Abstracts

Yiu-fai Cheung

Bryan Lin Professor in Paediatric Cardiology

Clinical Professor, Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong

Professor Yiu-fai Cheung is a clinician specializing in paediatric cardiology, a teacher, and a clinician investigator. He graduated from The University of Hong Kong in 1990, received his Doctorate of Medicine in 2004, became a full professor in The University of Hong Kong in 2007, and was awarded the Faculty Teaching Medal in the same year. He is currently Bryan Lin Professor of Paediatric Cardiology of the LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China.

Professor Cheung's research interests include ventricular function in congenital and acquired heart diseases, vascular health, and ventriculo-arterial interaction. His scope of research encompasses three domains: (i) paediatric and adult congenital heart disease, (ii) acquired heart disease in children, and (iii) vascular function in health and disease in the young.

His research work focuses on the followings:

- Clinical translation of novel echocardiographic imaging technologies
- Cardiac and vascular mechanics in paediatric and adult congenital heart disease,
- iron overload and chemotherapy toxicity
- Cardiac function after transcatheter and surgical interventions of congenital
- heart disease
- Circulating biomarkers in congenital heart disease
- Long-term clinical outcomes of paediatric congenital heart patients
- Kawasaki disease: genetics and vascular health
- He has written more than 150 peer-reviewed papers, 2 books, and 9 book chapters,
- produced a multimedia CD-ROM on diagnosis of congenital heart disease, and
- delivered more than 180 invited lectures.

At the Faculty level, Professor Cheung has been the Chairman of the Board of Studies of Master of Medical Sciences programme. At the Departmental level, he is member of the Education Committee and helps to coordinate undergraduate teachings of medical students. Externally, he is member of the Examination Committee of Hong Kong College of Paediatricians. He serves as examiner of the MBBS examinations, MRCPCH clinical examination, and Licensing Examination of the Medical Council of Hong Kong. Professor YF Cheung is responsible for the teaching of paediatric cardiology to medical students, paediatric residents, and cardiology fellows.

Professor Cheung provides specialist clinical service for children and adults with congenital and children with acquired heart diseases. Together with other paediatric cardiologists at Queen Mary Hospital, Hong Kong, he provides diagnostic evaluation, postoperative care, and transcatheter interventions for patients ranging from neonates with critical heart conditions to grown-up congenital heart patients.

The potential of human induced pluripotent stem cells to model and to treat congenital heart disease

Congenital heart disease is thought to have a multifactorial aetiology. While single gene mutation, copy number variations, and syndromic disorders in association with chromosomal aneuploidy and microdeletion are well known to be associated with various types of congenital heart disease, less than 15% of patients is found to have identifiable genetic aetiology in clinical practice. The complex interaction between genetics and environment contributes to the difficulty in pinpointing the primary underlying mechanism in the majority of patients. The emergence of the human induced pluripotent stem cell (iPSC) technology may, on the other hand, provide unique opportunities to dissect genetic mechanisms and signaling pathways that contribute to the high incidence of this human congenital malformation and to shed light on perturbation of myocardial function in the long term. The ability to generate human iPSC-derived cardiomyocytes from patients with cardiac disorders due to single gene mutation has provided an opportunity to model these cardiovascular diseases *in vitro* and to study their pathophysiological basis at molecular and cellular levels. Hence, several inherited cardiac conditions with single gene mutation, including channelopathies, arrhythmogenic RV dysplasia, and cardiomyopathies have been studied using this novel technology. Challenges exist, however, with regard to modeling of congenital heart diseases using the human iPSC technology. Notwithstanding, there are recent reports on the generation of iPSC model of hypoplastic left heart syndrome. Experimental studies have focused primarily on modeling of the right ventricle in the setting of pressure or volume overload. Of the limited clinical trials in patients with congenital heart disease, the focus is on hypoplastic left heart syndrome. Our group has recently generated iPSCs from patients with a spectrum of cyanotic heart disease. Cell-based tissue engineering with development of cell-seeded grafts and patches has begun. The preliminary data available to date suggest that human iPSC technology may shed light on better understanding of the genetic and cellular mechanisms and potentially become an adjunct to treatment of congenital heart disease.

Graduated from Birmingham University in 1995 with a PhD in biochemistry/ haematopoiesis and subsequently worked at IGBMC, Strasbourg; Oxford University and St Jude Children's Research Hospital, Memphis TN; before being appointed to the University of Glasgow in 2002. Background in the differentiation of normal and leukemic blood cells (1993-2008) and more recently (since 2008) has concentrated more on human pluripotent stem cells (hPSC).

Her academic interests are in the generation of mesodermal cell lineages for therapeutic use. This includes molecular and biochemical analyses and the overall aim is to fully dissect key signalling events, transcriptional networks and epigenetic changes that lead to effective differentiation to these lineages. She has successfully completed projects funded by the MRC, BBSRC, Wellcome Trust, EPSRC, Scottish Funding Council, Find a Better Way and the BHF.

In her role as Head of Cellular Therapeutics at the Scottish National Blood Transfusion Service Jo leads the development of novel cellular therapeutics from adult stem cells and hPSC including mesenchymal stromal cells (MSC), bone, endothelial and haematopoietic lineages. She has also developed, and leads, the SNBTS program for GMP generation, banking and testing of clinical-grade induced pluripotent stem cells (hiPSC).

Jo Mountford

Head of Cellular Therapeutics, Tissues Cells and Advanced Therapies, Scottish National Blood Transfusion Service

Hon. Associate Professor, Institute of Cardiovascular and Medical Sciences, University of Glasgow

Development of banking and testing protocols for GMP hiPSC

Induced Pluripotent Stem Cells (iPSC) offer huge clinical potential as a source of material for cellular therapies and tissue engineered products, however the realisation of this new generation of products is dependent on comparability between iPSC lines. Also, the idea that a single iPSC line would suffice as an intermediate material for the generation of cellular therapeutics for all patients ignores the problem of immunological incompatibility between donor and recipients leading to risks of immune rejection and the need for immunosuppression. Autologous iPSC could be used to avoid this problem but are likely to be prohibitively expensive at least in the first instance. Therefore, it may be more practical to generate clinical grade iPSC from a relatively small number of HLA homozygous individuals which would provide the closest match for the widest number of people in the global population. This will require international agreement and standards around issues such as donor selection, screening and consent, procurement of starting cells and tissues, iPSC generation and establishment of cell banks, quality control and regulatory compliance requirements.

I will discuss the challenges for procurement of tissue, generation of new GMP iPSC lines, genetic and safety testing and the issue of comparability if multiple lines are to be used to make the "same" cellular products for the treatment of highly prevalent diseases such as heart attack/failure, diabetes and neurodegenerative disorders.

Speaker Bios & Abstracts

Jean-Sébastien Hulot is Full Professor of Medicine, Pharmacology at Paris University, France. He is a medical cardiologist with a MD degree in clinical cardiology and a PhD degree in clinical and experimental pharmacology. In 2006, he was appointed as Associate Professor at Paris University and then served from 2010 to 2014 as an Associate Professor of Medicine, Cardiology at the Cardiovascular Research Center at Mount Sinai School of Medicine in New York, USA.

Since 2014, he is leading a research group at Paris University that is investigating the molecular, cellular and physiological mechanisms that lead to heart failure, with a particular focus on determinants of diastolic dysfunction and cardiac arrhythmias. The group has developed new heart failure models based upon human iPS cells, particularly focusing on defective calcium mechanisms that trigger deficient contractility as well as relaxation. The team has also developed a hiPSC platform to better characterize the individual predisposition to develop drug-induced cardiac arrhythmias. In parallel, Dr Hulot's team is investigating the potential of genome editing *in vitro* in human induced pluripotent stem cells and *in vivo* to propose new therapeutic approaches for inherited cardiomyopathies.

Jean-Sébastien Hulot was appointed a Fellow of the European Society of Cardiology in 2014. He is the president-elect of the Basic and translational research group of the French Society of Cardiology, and since 2016 Member of the Translational research committee of the Heart Failure Association of the ESC.

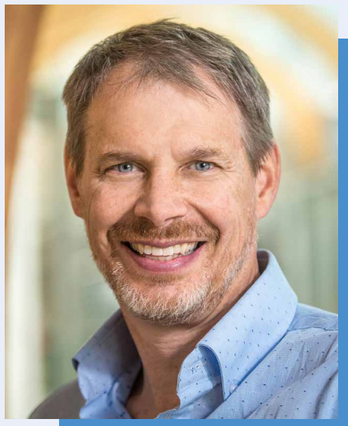
The projects are funded through the French National Agency for research (ANR), the European Commission (Era-NET H2020), and the Leducq Foundation (Transatlantic networks of excellence 2018).

Jean-Sébastien Hulot

Team Leader, Clinical & Translational Investigation Center, Hôpital Européen Georges-Pompidou (Hôpitaux Universitaires Paris-Ouest) Paris Cardiovascular Research Center PARCC / INSERM

Predicting individual arrhythmogenic risk at the individual level using hiPSC

Certain individuals have increased propensity to develop prolonged QT interval and consequent life-threatening ventricular arrhythmias in response to drugs that alter cardiac ion currents, notably the IKr. The risk of arrhythmia can be further elevated in the presence of (i) acquired factors (e.g., ionic disturbances) and (ii) genetic factors (e.g., underlying mutations). We have recently demonstrated *in vitro*, the potential of patient-specific iPSC-CMs to recapitulate their *in vivo* predilection to develop diLQTS. This patient-specific iPSC-CMs library can thus be use to better predict the arrhythmogenic risk of drugs at the cellular level (drug screening assays) and proposes a new strategy to better predict risk at the patient level (precision medicine). We also show how iPSC can further be used to model "clinical trial in a dish" (population level) to better guide experimental drug testing in enrolled patients.



Peter Zandstra

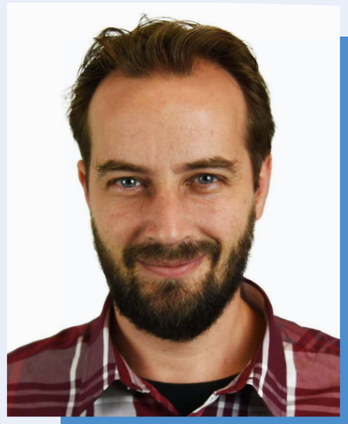
Director, School of Biomedical Engineering, The University of British Columbia

Peter Zandstra graduated with a Bachelor of Engineering degree from McGill University in the Department of Chemical Engineering, obtained his Ph.D. degree from the University of British Columbia in the Department of Chemical Engineering and Biotechnology and continued his research training as a Post-Doctoral Fellow in the field of Bioengineering at MIT. In 1999, Dr Zandstra began his faculty appointment at the University of Toronto's Institute of Biomaterial and in 2016 was appointed University Professor, the university's highest academic rank. In July 2017, Zandstra joined the University of British Columbia as the Founding Director the School of Biomedical Engineering and as the Director of the Michael Smith Laboratories. In these roles, he aims to build programs with deeper interactions between the Faculties of Applied Science, Science and Medicine, especially as related to innovative research and training programs.

Peter is the Canada Research Chair in Stem Cell Bioengineering and is a recipient of a number of awards and fellowships including the Premiers Research Excellence Award (2002), the E.W.R. Steacie Memorial Fellowship (2006), the John Simon Guggenheim Memorial Foundation Fellowship (2007), and the University of Toronto's McLean Award (2009). Dr Zandstra is a fellow of the American Institute for Medical and Biological Engineering and the American Association for the Advancement of Science. Peter's research focuses on understanding how complex communication networks between stem cells and their progeny influence self-renewal and differentiation, and how this information can be applied to the design of novel culture technologies capable of controlling cell fate.

Engineering cardiac tissue and development

Speaker Bios & Abstracts



Luke MacQueen

Postdoctoral Fellow, Bioengineering in the Wyss Institute, Harvard University

Luke MacQueen is a research associate in the Disease Biophysics Group led by Professor Kevin Kit Parker at Harvard University, where he builds tissue engineered laboratory models of human organs with a focus of muscle tissues. Prior to his work at Harvard, Luke obtained his PhD in Engineering Physics from the Ecole Polytechnique in Montreal and then worked as a postdoctoral researcher at the University of Toronto in the field of cellular mechanobiology. Luke's research interests include material sciences and device physics that enable our use of biological cells as 'building blocks' for tissue engineering microphysiological systems, regenerative medicine research, and emerging bioprocess applications.

A tissue-engineered scale model of the heart ventricle

Preclinical cardiology and regenerative medicine research will benefit from an expanding set of *in vitro* models where human heart structure and function are examined at multiple scales. Here, we report a tissue-engineered scale model of the human left ventricle, made of nanofibrous scaffolds that promote native-like anisotropic myocardial tissue genesis and chamber-level contractile function. Taking design inspiration from mammalian myocardial tissue architecture, we hypothesized that ventricle-shaped scaffolds composed of nanofibrous materials would promote cardiomyocyte assembly into functional 3D ventricle chambers that could be evaluated with the same assays used in animal models and in clinical settings. To test this hypothesis, we cultured nanofibrous polycaprolactone (PCL)-gelatin scaffolds with rat or human cardiomyocytes, measured tissue coverage and alignment, calcium-transient propagation over the ventricle surface, and intra-ventricular pressure/volume loops in the presence or absence of test compounds. Ventricle chamber scaffolds with anisotropic fiber alignment promoted cell infiltration and anisotropic muscle tissue formation, as verified by immunohistochemical staining. The resulting tissues formed an electromechanical syncytium, supporting calcium wavefront propagation observed by optical mapping on the ventricle surface and synchronous contraction measured by pressure-volume catheterization. A proof-of-concept structural arrhythmia disease model demonstrated that stable pinned spiral waves could be generated on ventricle surfaces by inflicting geometrically controlled injuries. We then built an instrumented bioreactor with optional valve inserts and ventricular assist capabilities to support ventricle culture and in situ functional evaluation. We measured pressure-volume dynamics by catheterization and ventricle wall displacement by echocardiography using ventricles that were cultured in our bioreactor or in standard well plates. Our results demonstrate the feasibility of engineering functional scale models of the heart chambers and our use of small animal cardiology assays for model ventricle performance evaluation suggest that patient-derived scale models of the heart chambers can be tested in existing pre-clinical settings, where animal models are currently used. Our design rules provide a path towards engineering model heart chambers with functional performance increasingly comparable to native organs.

Robert DeVita

Director of Medicinal Chemistry,
Drug Discovery Institute

Professor, Department of
Pharmacological Sciences,
Icahn School of Medicine at Mount Sinai

Dr Robert DeVita, Ph.D. is a Professor at the Icahn School of Medicine at Mt. Sinai in the Departments of Pharmacology and Systems Therapeutics and Structural and Chemical Biology. He is also the Director of Medicinal Chemistry for the Drug Discovery Institute (DDI). Dr DeVita is developing small molecule drug discovery projects in collaboration with principal investigator labs in the Mt. Sinai research community. Current NIH funded projects include research directed toward discovering new therapeutics for diabetes, cardiovascular, cancer and orphan disease indications.

Prior to joining Mt. Sinai in 2014, Dr DeVita gained expertise managing multi-disciplinary teams that delivered on key program objectives for complex molecular targets. He has over 25 years' experience working in biotech (VP of Chemistry at Agios, 2012-2013) and the pharmaceutical industry at Merck Research Laboratories where he was a director of medicinal chemistry from 2004-2012. He was trained as an organic synthetic chemist earning his Ph.D. at University of Rochester followed by a N.S.F. Postdoctoral at the University of Geneva. He started his professional career at Merck in 1990.

Dr DeVita's work has spanned the drug discovery paradigm from target identification to PII clinical studies, including leadership of drug development teams. In collaboration with multi-disciplinary discovery teams, he has identified numerous development candidates including two PII clinical compounds for Central Nervous System (NK1) and Cardiovascular (NPC1L1) targets. Dr DeVita has drug discovery experience within a broad range of therapeutic areas including: CNS, pain/inflammation, diabetes, cardiovascular, hypertension, obesity, endocrinology, urology and oncology. He has developed, in collaboration with his teams, orally active, brain penetrant, peripheral and GI-tract small molecule drug targeting strategies. He also has experience in the discovery and development of PET imaging agents and translational biomarkers for CNS targets including FAAH.

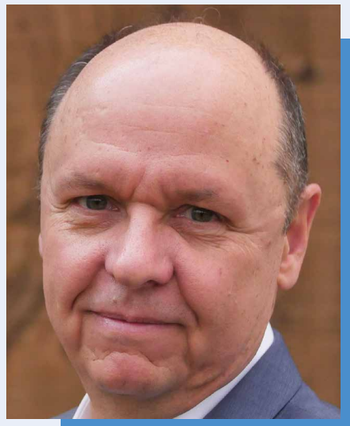
Dr DeVita has been an active member of the Medicinal Chemistry Division of the American Chemical Society serving on the Long Range Planning Committee and on the organizing committees for National and International Medicinal Chemistry Meetings. He has served as an Ad Hoc Reviewer for the National Institutes of Health Study Section for Synthetic and Biological Chemistry (Section B) and National Institute of Diabetes, Digestive and Kidney Diseases. He also consults for academic, biotech, legal, pharma and venture capital clients.

Small molecule drug discovery, transitioning from industry to academia: SERCA2a SUMO activators for heart failure

Many academic institutions are expanding their basic research approaches to begin "translational" aspects of drug discovery, an activity that is now under supported in the pharmaceutical industry. We will briefly present the translational strategy for target selection, discovery program initiation to development and long term vision to create a sustainable, small molecule portfolio in the Drug Discovery Institute at Mt Sinai. Some of the challenges and opportunities for academic drug discovery will also be discussed.

As a case study, the details on the validation of small molecule activators of SERCA2a SUMOylation as therapeutics for the treatment of heart failure will be presented. SUMOylation is an important regulator of the functional properties of proteins. SUMOylation is also associated with specific human diseases where proteins are differentially SUMOylated and become dysregulated. We found that activity and protein stability of cardiac sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a), an enzyme critical for cardiac function, are modulated by small ubiquitin-like modifier type 1 (SUMO1). Furthermore, we showed that increasing SUMO1 levels led to the restoration of SERCA2a levels, improved hemodynamic performance, both in mice and pig models of heart failure. We identified and characterized a small molecule, N106, which increases SUMOylation of SERCA2a. This compound directly activates the SUMO-activating enzyme E1 (SUMO E1) and triggers intrinsic SERCA2a SUMOylation. Importantly, we identified a pocket on SUMO E1 likely to be responsible for N106's effects. N106 treatment increased contractile properties of isolated cardiomyocytes and significantly improved ventricular function in mice with heart failure. More recently, our medicinal chemistry effort focused on lead candidate identification to successfully find TB01B, an analogue of N106. TB01B has increased potency, improved drug metabolism and pharmacokinetic profile with minimal off-target activity. TB01B acutely and chronically improve cardiac contractile properties in heart failure mice. Formulation and preclinical studies for TB01B are being developed for future human clinical trials. Together, these findings suggest that (N106)/TB01B might be a novel therapeutic option for the treatment of heart failure.

Speaker Bios & Abstracts



Bernard Fermini

Co-chair, CiPA Ion Channel Working Group of the U.S. Food and Drug Administration

Bernard Fermini received a Ph.D. in Biophysics from the University of Sherbrooke (Canada), and completed post-doctoral training at Texas Tech University Health Sciences Center. He joined the Montreal Heart Institute (Canada), and focused his work on cardiac electrophysiology where he led a team in the discovery of a novel atrial selective K+ ion channel. Bernard then moved to Merck in PA and worked on atrial antiarrhythmic agents before joining Pfizer in Groton, CT, where he held positions of increasing responsibilities including Associated Director of Global Safety Pharmacology, and Head of the Ion Channel Discipline. He then joined Coyne Scientific as Vice President of Safety and Toxicology Assessment and Chief Scientific Officer where he focused on the role of genetic diversity in adverse drug reactions. He is currently the Chief Research & Development Officer at Novoheart where he leads its industrial expansion in drug discovery and development, leveraging his extensive experience and networks in the pharma industry.

Since 2013, Dr Fermini has been the Co-chairman of the Ion Channel Working Group of the Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative, headed by the US Food and Drug Administration (FDA). As Co-chair, he oversees the research into identifying next-generation screening methods for effective detection of drug-induced cardiac arrhythmias before clinical trials. Dr Fermini is also a Board Member on the CiPA Steering Committee, co-chair of the Student and Jr. Investigators Travel Award of the Safety Pharmacology Society (SPS), member of the SPS Publication Awards Committee, previous member of the Board of Directors of SPS, as well as an active member of Health and Environmental Sciences Institute (HESI) Cardiac Safety Committee, and the Society of Toxicology.

Stem cell cardiomyocytes in drug discovery and development – are we there yet?

Cardiomyocytes from human pluripotent stem cells (hPSCs-CMs) hold the promise of revolutionizing biomedicine. Indeed, advances in hPSC isolation, genome engineering and hPSC-CM differentiation have contributed to improved patient care, and to progressing drugs to the clinic, opening a new era in safety pharmacology. Nonetheless, predictive cardiotoxicity using hPSC-CMs remains an evolving science as both failure and success has been reported in the literature. Certainly, iPSCs offer the possibility to generate patient-specific stem cell lines from individuals affected by inherited disorders, and cardiomyocytes differentiated from such patients have been used to study the pathophysiology of arrhythmogenic heart diseases, to test for unwanted drug side effects or for tailoring medical treatment to the specific needs of individual patients. In this presentation we review the strengths and limitations of the current vintage of iPSC-CMs as models in drug discovery and development, and consider future advances potentially needed for the more widespread adoption of hPSC-CMs in the pharmaceutical industry.

At Nanion Technologies since 2005. Current position: Director, Scientific Affairs at Nanion Technologies GmbH, Munich, Germany.

Since 2016 Co-Chair of the CiPA HTS (High throughput screening) ion channel working group and involved in the CiPA myocyte working group.

2000-2004 Ph.D. thesis in the lab of Prof. Dr. R. Hedrich, at the Department of Molecular Plant Physiology and Biophysics, Julius-von-Sachs-Institute for Biological Sciences, University of Wuerzburg, Germany. Topic: Light- and Redox-Regulation of Calcium permeable Channels in Arabidopsis thaliana Mesophyll Cells.

1995-1999 Studies of Biology (Diploma) at University of Ulm and Julius-Maximilians-University, Wuerzburg, Germany. Main topic: Plant Physiology. In addition: Biochemistry and Pharmaceutical Biology.

Approx. 20 Publications in the field of automated patch clamping, cell physiology and cardiac safety (https://www.linkedin.com/in/sonja-stölzle-feix-96472514/)

Sonja Stoelzle-Feix

Director Scientific Affairs at Nanion Technologies

Co-chair, CiPA Ion Channel Working Group of the U.S. Food and Drug Administration

New challenges in safety pharmacology

In the ever-evolving world of safety pharmacology, adequate tools and strategies are not only preferred but necessary. Ion channels have long been targets for various safety testing. However, other proteins involved in the transport of ions across membrane barriers are becoming increasingly relevant for pharmacological safety. Additionally, the need for high throughput measurements moved the industry demand towards automated systems.

Here, we focus primarily on the development and applications of such automated technologies in cardiac safety testing, as done during the Comprehensive *in Vitro* Proarrhythmia Assay (CiPA) initiative introduced by FDA. This initiative is focused on proarrhythmia to improve specificity compared to *in vitro* hERG and *in vivo* QT studies. We combined automated patch clamp (APC), impedance and extracellular field potential (EFP) measurements in order to study cardiac ion channels in cell lines and hiPSC-derived cardiomyocytes (hiPSC-CMs). Data emphasizing protocols, ease of use and results obtained in this initiative will be presented. To drive the progress of pharmacological investigations, of not only ion channels but of cardiac transporters as well, we have developed a novel, solid supported membrane (SSM) - technology based device. Here, we will also show measurement comparisons of data obtained from cell lines and hiPSC-CMs.

In conclusion, by providing automated high-throughput systems with cross-site and cross-cell stable recordings, using open data and analysis concepts, valuable and powerful solutions for safety pharmacology, as well as drug development efforts, are emerging.

Speaker Bios & Abstracts

Prof Costa is one of the scientific co-founders of Novoheart, and has served as the CSO since 2017. He is Director of Cardiovascular Cell and Tissue Engineering at the Icahn School of Medicine at Mount Sinai in New York City, and was previously trained at the Johns Hopkins University and on the faculty as Associate Professor of Biomedical Engineering at Columbia University. As a “blue-blood” biomedical engineering (BME) expert (B.S. and M.S. in BME from Boston University, Ph.D. in BME from UC San Diego, and postdocs in BME from JHU and Washington University) in cell and tissue biomechanics and cardiac tissue engineering, he has developed one of the first engineered cardiac tissue systems and is an inventor of several cardiac tissue engineering technologies. Since 2009, he has been working with Prof Ronald Li to translate such systems into human cells. Prof Costa has received research funding from the Whitaker Foundation, the National Science Foundation (NSF) and the National Institutes of Health (NIH; NHLBI, NIBIB, and NIGMS). He was also a recipient of the prestigious Faculty Early Career Development (CAREER) Award from the NSF.

Kevin Costa

Co-founder and Chief Scientific Officer, Novoheart

Toward a precision medicine approach to drug screening using Novoheart’s hPSC-based MyHeart™ Platform

Traditional drug discovery suffers from a longstanding gap in the ability of pre-clinical animal studies to predict human clinical outcomes, resulting in high late-stage failure rates of drugs that are often related to unexpected cardiotoxicity. Post-market withdrawals due to low-incidence patient-specific adverse drug responses carry additional societal and economic burdens and erode public confidence in the pharmaceutical industry and federal regulatory agencies. To fill this gap and improve the drug discovery process, Novoheart has developed its proprietary MyHeart™ Platform of bioengineered cardiac assays created using pluripotent stem cell-derived human ventricular-like cardiomyocytes (hvCM). This Platform includes the cardiac anisotropic sheet (hvCAS) for testing arrhythmogenicity, the cardiac tissue strip (hvCTS) for testing contractility, and the cardiac organoid chamber (hvCOC) with sufficient biological complexity to capture key electrophysiological and contractile properties of the heart; this “mini human heart-in-a-jar” uniquely provides integrated pressure and volume based measures of global pump function such as ejection fraction, developed pressure, cardiac output, and stroke work, that are readily interpreted in the context of clinical cardiology. This presentation will review the capabilities of the individual MyHeart™ Platform assays, with examples using healthy hvCMs for testing cardiotoxicity as well as hvCMs with specific genetic abnormalities for disease modeling and testing drug efficacy. Extension to using patient-specific hvCMs for a precision medicine approach to drug screening will also be discussed.

An entrepreneur, engineer, inventor, Tamer currently serves as Aspect Biosystems' President and Chief Executive Officer. Tamer co-founded Aspect in 2013 and has played a leading role in its overall corporate, business, and technology development. Under his leadership, Aspect has secured significant funding, entered strategic collaborations with best-in-class pharmaceutical and biotechnology companies, and developed its commercial products. In his previous appointment as Chief Technology Officer of the company, Tamer drove the innovation and development of the company's core technologies and intellectual property. As a leader in the field of 3D bioprinting, he has been invited to speak on this topic at venues ranging from TEDx to industry, scientific and executive conferences. In 2017, he was awarded BC's Top 40 under 40 award for demonstrating excellence in business, judgement, leadership, and community contribution. Tamer serves on the Board of Directors for ACETECH, a non-profit training and mentoring organization for CEOs of technology and life sciences companies, and on the Board of Directors for The Stem Cell Network, an organization focused on building Canada's stem cell and regenerative medicine research sector. Tamer holds a B.A.Sc. in Biomedical Engineering and M.A.Sc. in Electrical and Computer Engineering from the University of British Columbia.

Tamer Mohamed

President and Chief Executive Officer,
Aspect Biosystems

Collaborating to create engineered human tissues using 3D bioprinting technology

3D bioprinting technology holds the immense potential to significantly impact field of regenerative medicine. But the technology itself is just one piece of the puzzle. At Aspect Biosystems, we are combining our unique Lab-on-a-Printer™ bioprinting technology with the specialized knowledge of academic and industry experts to generate functional 3D tissues for pre-clinical drug discovery and as implantable therapeutic tissues to cure diseases. CEO, Tamer Mohamed will discuss how Aspect collaborates to develop these engineered human tissues and the significant potential they hold to accelerate therapeutic discovery and regenerative medicine.

Speaker Bios & Abstracts

Emily is Vice President, Technology Advancement at CCRM. She obtained her PhD from the Institute of Biomaterials and Biomedical Engineering at the University of Toronto, where she used a combination of laboratory and bioinformatics approaches to define and interpret gene regulatory networks controlling embryonic stem cell fate decisions. At CCRM, Emily's team sources, develops and evaluates technology related to iPSC derivation, cellular immunotherapies, genome engineering, directed differentiation and translation of bench scale protocols to scalable platforms, and works on projects that advance the commercialization of stem cells. Most recently, she has established the company creation program at CCRM that will incubate and spin-out companies focused on novel cell and gene therapies.

Emily Titus

Vice President, Technology
Advancement, Centre for
Commercialization of Regenerative
Medicine (CCRM)

Scale-up of pluripotent stem cell production to enable translation and commercialization

Speaker Bios & Abstracts

Sabrina Chan

Senior Executive Director, The Hong Kong Association of the Pharmaceutical Industry

Sabrina is the Senior Executive Director of the Hong Kong Association of the Pharmaceutical Industry (HKAPI); member of the High Level Steering Committee on Antimicrobial Resistance; member of Business Facilitation Advisory Committee; Chair of Advisory Board of the HKU Bachelor of Pharmacy Program, Adjunct Assistant Professor of CUHK School of Pharmacy; and member of APEC Biopharmaceutical Working Group on Business Ethics.

Prior to joining the pharmaceutical industry, she was with the External Affairs Department of i-CABLE Communications Ltd. and was responsible for government relations, regulatory issues, corporate affairs, and the promotion of the company's core products and services. She co-founded the Telecommunications Research Project under Centre of Asia Studies (HKU), and was a journalist at various print and electronic media outlets.

Sabrina studied Communications in Hong Kong when she began her tertiary education. She holds a graduate degree in International Studies from the University of Sheffield (UK), as well as law degrees from the CUHK and University of Tsinghua (China).

About HKAPI:
Formed in 1968, HKAPI has 39 full members, including the world's top 20 companies engaged in pharmaceutical R&D. Its member companies provide over 70 per cent of prescription medicines in Hong Kong. The Association's mission is to drive the expedient access to innovative healthcare solutions for the people of Hong Kong and Macau with high ethical standard. It also aims to help transform the healthcare ecosystems in Hong Kong and Macau "from good to great".

Where is Hong Kong in developing precision medicine?

Mrs. Carrie Lam, Chief Executive of HKSAR, has pledged to promote the development of innovation and technology as the city's future economic driver and biomedical technology is one of the key areas. This year, the government has put forth a preliminary recommendation to conduct a large-scale genome sequencing project in Hong Kong to enhance the clinical application of genomic medicine. The project also aims to promote innovative scientific research on genomic medicine to cater for future medical development in Hong Kong through the establishment of genome data of local population, testing infrastructure and talent pool. What is needed more? – from industry's perspective.

Notes

Dr Li Dak-Sum Research Centre
李達三博士研究中心

Ming Wai Lau Centre
for Reparative Medicine
劉鳴煒復修醫學中心

Karolinska Institutet

This workshop is sponsored by a Seed Funding Scheme from Dr. Li Dak-Sum Research Centre, The University of Hong Kong – Karolinska Institutet Collaborations in Regenerative Medicine, The University of Hong Kong (Project No. [LDS-SoW-2016/17]).